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Informed Choice in Fragile X Syndrome and Its Effects on Prevalence

H. Robinson, S. Wake, F. Wright, S. Laing, and G. Turner

Fragile X Program, Prince of Wales Children's Hospital, Sydney (H.R., S.W., F.W., S.L.); and Hunter Genetics Service, Newcastle (G.T.), New South Wales, Australia

We present the effect of case finding, cascade testing, and counselling for fragile X syndrome in a population of 6.5 million over a decade. Carrier females made informed choices that resulted in a 10-fold decrease in the prevalence of affected males in their offspring. © 1996 Wiley-Liss, Inc.

KEY WORDS: prevalence, counselling, effects, fragile X

"Genetic screening should enable people to escape their fate by giving them the freedom to make an informed choice and adopt a chosen course of action which they regard as acceptable." Health Council of the Netherlands, Committee of Genetic Screening, 1994.

INTRODUCTION

Until the mid-1970's the association of X-linked patterns of inheritance with mental handicap was seldom considered in the genetic counselling of families with mental retardation. Clustering of developmental problems in families was loosely attributed to cultural/familial causes. However, this was changed by the recognition of fragile X syndrome, its clinical definition, its mode of inheritance, and the development of a cytogenetic test to confirm the diagnosis, all of which drew attention to the major importance of genes on the X chromosome in the cause of mental retardation [Turner et al., 1978].

In 1977 the identification of a fragile site at Xq27.3 became a reasonably reliable test for both males and females with fragile X syndrome and mental retardation. This allowed formulation of a diagnosis and its mode of inheritance, even in singleton families, but did not identify those individuals of both sexes who carried the premutation and were not mentally retarded. These could only be identified by pedigree data which, in the case of the normal transmitting male, required identification of fragile X syndrome in his daughter's children. Prenatal diagnosis based on finding the fragile site was reliable for detecting affected males from 1980 onwards in New South Wales (NSW), providing families with a new alternative. This made it more important for families to have the "right to know," and motivated case-finding in the community.

In 1984 a program to screen the mentally handicapped population in NSW was started. This has developed over the years [Turner et al., 1986, 1992] from a pilot to a statewide program. In 1990 molecular methods became available, allowing more accurate diagnosis and identification of clinically unaffected fragile X carriers. In this paper we examine the effects of the introduction of cytogenetic and molecular methods on the reproductive decisions of women in fragile X families.

MATERIALS AND METHODS

In NSW, with a population of 6.5 million, 195 families with fragile X syndrome are known. All families from the state are referred to the program for molecular investigation and family counselling. These families have been diagnosed and their members counselled since the late 1960's. Initially a few families were counselled purely on the basis of a pedigree demonstrating X-linked inheritance of mental handicap [Turner et al., 1971, 1972]. In the early 1970's, the families of pairs of brothers in an institution were interviewed [Turner et al., 1992] and information was given about X-linked patterns of inheritance if there was supportive pedigree information. Four families in this group later turned out to have fragile X syndrome. In 1970 macroorchidism [Turner et al., 1974] was recognized as a manifestation of an X-linked pattern of inheritance. Three families were counselled on this basis. In 1977 the cytogenetic method of identifying an X-linked cause of mental handicap led to the recall of 16 X-linked families, and six families were identified as having fragile X syndrome. Over that time a number of other families with mental handicap showing an X-linked pattern of mutations were referred and counselled on that basis. From 1977 onwards we were able to confirm cytogenetically fragile X syndrome and offer appropriate counselling those families, even if only a single person was affected. In 1978 [Turner et al., 1980] we started a research screen-

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Address reprint requests to Prof. G. Turner, Hunter Genetics, P.O. Box 84, Waratah 2298, New South Wales, Australia.

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ing program in mildly mentally handicapped girls; 128 girls were screened, and five families were identified and counselled. In 1983 [Turner et al., 1986] we screened all the mentally handicapped in a population of 1.1 million. Forty families were identified and counselled on the basis of cytogenetic data. Between 1986–1988 in a statewide screening program, all individuals identified as being intellectually handicapped were offered the opportunity for physical examination and testing. Two hundred and fifty-three probands were identified [Turner et al., 1992] and the families were counselled. In 1990, when molecular testing became available, families were offered reinvestigation, so that definitive carrier status could be identified. This period led to the identification of a number of normal transmitting males and to the counselling and investigation of their obligatory carrier daughters and in some cases the identification of unrecognized affected male infants. During this period, pedigrees were maintained, a cross-reference system for family names was introduced, and a register was started with the onset of molecular testing. The families were contacted yearly and pedigree information was updated. A yearly newsletter was sent to those on the register. In all pedigrees we recorded the year in which the information of the X-linked nature of the inheritance in the family was explained. During the period when cytogenetic data were used for counselling, the normal males in the family were not counselled on the basis of their offspring being at significant risk, and no attempt was made to counsel the daughters of normal males in the pedigree.

In the 195 fragile X families there are 425 living affected males, and 541 females identified as carriers based on molecular testing (221 of these were at risk of being carriers but were cytogenetically negative and not obligate carriers).

One hundred and nine normal transmitting males are identified, 83 by DNA testing and 28 from pedigree data or by identification of the wife being negative on molecular testing. In general we do not test children unless their parents insist, or if the girls are having learning problems at school.

From 1980 all were offered prenatal diagnosis by cytogenetic testing through chorionic villus biopsy, and patients were informed that we were of the opinion that this was a reliable test. The reproductive pattern of five overlapping groups of women was studied.

Group 1

This group consisted of all women in fragile X families (excluding those counselled that their family might have an X-linked condition prior to 1977) who from pedigree evidence were obligate carriers or at 50% or at 25% risk of being carriers. The number of children born to these women prior to 1977 was compared to that of women of the same age in the general population of NSW.

Groups 2 and 3

All of these women were followed up in 1990, with a review of their reproductive decisions prior to molecular testing. These findings were published in Turner et al. [1992].

Group 2. All women from the fragile X families born between 1945–1975 who had a first-degree relative with fragile X syndrome comprised this group. Of 417 such women we were able to follow 387 (93%) and obtain information about their level of intellectual functioning, whether normal or with some degree of handicap (as judged by reported school performance or family opinion), and about that of their families and offspring. Each woman was designated a case, and the study period was from the year she had received genetic counselling to the year of follow-up.

Group 3. These were the controls. They were from the same 387 women with a first-degree relative with fragile X syndrome. They were selected women who had received genetic counselling at an age above that at which a matched case was followed up. Thus, the reproductive pattern during a particular age of the case was compared with that of the same age span of a control subject who at that time had not been counselled. Each case and control were matched for level of intellectual functioning and for whether they had lived with an affected male and whether they had given birth to at least one affected child before the study. It was possible to match up 230 case/control pairs.

Group 4

These consisted of all females in all pedigrees found to be carriers based on molecular testing. Their reproductive decisions from 1990–1993 were examined.

Group 5

These were women who had a son identified as having fragile X syndrome. Their reproductive patterns from 1990–1993 were examined.

Information was gathered by both direct and telephone interviews, regarding the reproductive decisions and outcomes of relatives even if they had not wished molecular testing. The information is thought to be relatively complete in those families that have a member on the register, concerning the birth of sons and whether they were affected.

RESULTS

The reproductive performance of women in group 1 is shown in Figure 1. There were few differences from that of the general population in NSW, except for a reduced birth rate among older women in the fragile X families.

Figure 2 compares the number of pregnancies of the women in group 2 with those of group 3 i.e., in similar groups of women with and without genetic counselling. It can be seen that the group of counselled women had a significant drop in birth rate from 104 to 77 ($\chi^2 = 4.03$; df = 1; $P < 0.05$) with 61% utilising prenatal diagnosis.

Figure 2 also compares the pregnancy rate of group 2 with that of group 4, and indicates increasing use of prenatal diagnosis once carrier status was defined. Also in Figure 2, the uptake of prenatal diagnosis was 91% in a smaller group of women who already had a son with fragile X syndrome (group 5).

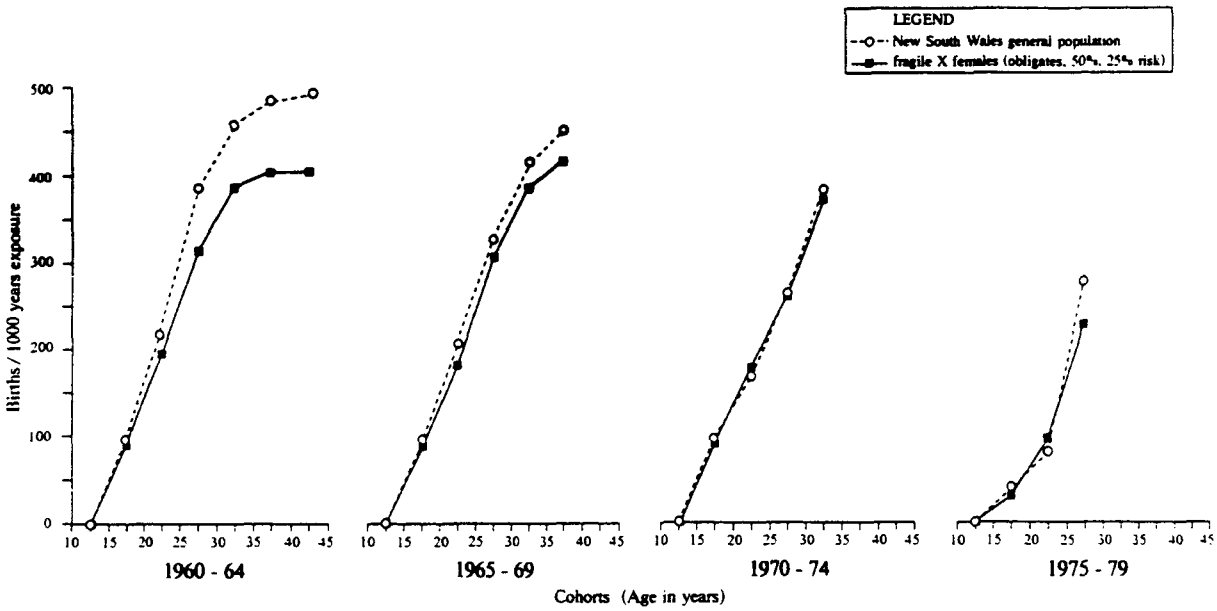

Fig. 1. Comparison of birth rates of women in fragile X families (group 1) with the general population.

The birth incidence of fragile X males, together with affected pregnancies which were terminated, from 1980–1993 is shown in Figure 3.

DISCUSSION

It is of great interest that before genetic counselling was widespread, the presence of mental retardation in a family did not appear to influence decisions about having children [Partington, 1986], at least in women under age 30 (Fig. 1). Fewer pregnancies beyond this age might be explained by an active decision based on stress caused by children with intellectual handicap in the family, or it may reflect a decline in fertility secondary to the earlier onset of menopause in fragile X carriers [Schwartz et al., 1994; Partington and Turner, 1996].

The diagnosis of fragile X syndrome and counselling about its mode of inheritance, together with an assess-

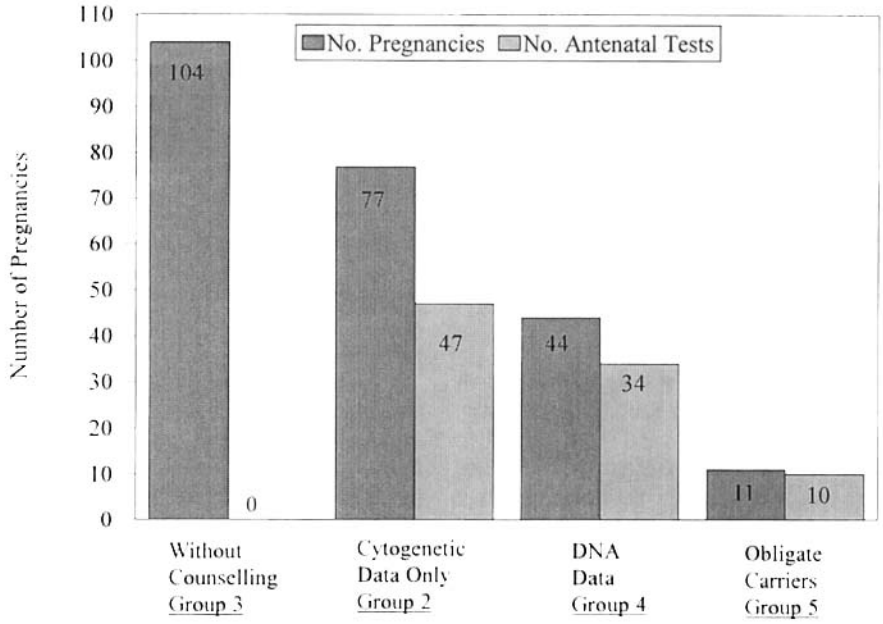

Fig. 2. Pregnancies and prenatal diagnosis in women from fragile X families who had not been counselled (group 3), compared with a matched group (group 2) who had been counselled on pedigree and cytogenetic data, and with a group whose carrier status had been established by DNA methods (group 4). The uptake of prenatal diagnosis in obligate carriers with an affected son (group 5) is also shown.

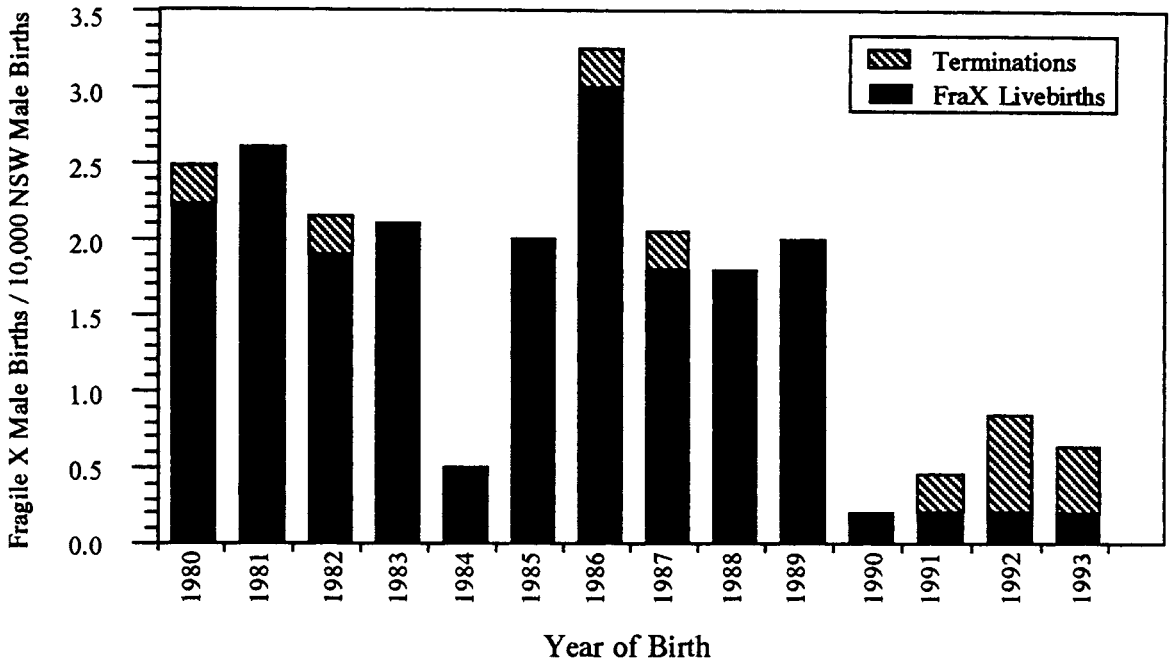

Fig. 3. Combined birth prevalence and prevalence found by prenatal diagnosis of fragile X syndrome in New South Wales, by year, from 1980–1993.

ment of the risk of carrier status, resulted in a decrease in the number of pregnancies by 26%, with 61% being monitored by prenatal diagnosis (Fig. 2). Definitive DNA diagnosis after 1990 showed that a number of these women were not fragile X carriers and so eliminated the need for their pregnancies to be monitored. By the same token, in others, fragile X carrier status was confirmed. Most such women opted for prenatal diagnosis in subsequent pregnancies (Fig. 2).

The overall reduction in the birth incidence of affected fragile X males in these families (Fig. 3) showed a 10-fold decline, reflecting both a reduction in birth rate as well as termination of affected pregnancies. We believe that reproductive confidence in carrier females is being reestablished, as shown by increased uptake of prenatal diagnosis.

In our experience, decisions about whether to embark on a pregnancy, about the use of prenatal diagnosis, and about whether or not to terminate electively in these families are comparatively straightforward for the sisters or cousins who are in regular contact with an affected male. Some decide to have no children, others wish prenatal diagnosis, and a small proportion, usually females with the full mutation, have unmonitored pregnancies: the mothers of this group are a significant influence on decisions. The problems posed by identifying a female with a full mutation by prenatal diagnosis and her subsequent risk of having learning problems or mental handicap are always discussed prior to testing. Parents are encouraged to make decisions before test results become available. For those whose chorionic villus biopsy results identify a female with the full mutation, 60% opted for termination and 40% decided to continue the pregnancy.

The birth prevalence shown in Figure 3 is the birth prevalence in all identified families. We think that the observed birth prevalence reflects at least 80% of the general population prevalence. The observed prevalence in most of the last 20 years matches the calculated prevalence of an uncounselled population [Turner et al., 1996]. The decisions that families made should have been reflected in a decline in 1988–1989. We think the lack of decline in those years, followed by a large drop, is due to the identification of a number of older transmitting males by molecular studies, which started in 1990. In this manner a number of their daughters were identified who had young children with developmental delay who, on testing, were positive, explaining the new group of young fragile X boys. There will be new families with young children who have not been identified, so that the low rates of 1990–1993 are likely to rise, but certainly not to previous levels. The Fragile X Program has made individuals providing early intervention services and the school staff much more aware of this condition, and continued screening in schools may no longer be appropriate in NSW. However, screening may still be very appropriate in other regions or countries that have had no such program of index case identification and active cascade testing.

Genetic service providers should consider seriously establishing such a community program of case-finding. We would recommend strongly the employment of trained and dedicated genetic counsellors to provide such a service.

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